

# *Acta Medica Okayama*

---

*Volume 34, Issue 5*

1980

*Article 7*

NOVEMBER 1980

---

## Treatment of refractory acute leukemia with aclacinomycin-A.

Isao Takahashi, *Okayama University*  
Masamichi Hara, *Okayama University*  
Tomiro Adachi, *Okayama University*  
Kazuko Takaoka, *Okayama University*  
Makoto Sakano, *Okayama University*  
Miinyuh Lai, *Okayama University*  
Fumikazu Kohi, *Okayama University*  
Seiichi Yorimitsu, *Okayama University*  
Masaaki Tokioka, *Okayama University*  
Koichi Kitajima, *Okayama University*  
Ikuro Kimura, *Okayama University*  
Hiroshi Sanada, *Okayama University*

# Treatment of refractory acute leukemia with aclacinomycin-A.\*

Isao Takahashi, Masamichi Hara, Tomiro Adachi, Kazuko Takaoka, Makoto Sakano, Miinyuh Lai, Fumikazu Kohi, Seiichi Yorimitsu, Masaaki Tokioka, Koichi Kitajima, Ikuro Kimura, and Hiroshi Sanada

## Abstract

Twelve patients with refractory acute leukemia (7 patients with acute myelocytic leukemia and 5 patients with acute lymphocytic leukemia) were treated with a new anthracycline antibiotic, aclacinomycin-A (ACM). ACM was administered by intravenous drip infusion at a dose of 20 mg/day for 7 or 14 days and this was repeated after at least 7 days. Four of 12 patients (33.3%) achieved a complete remission; 3 of 7 acute myelocytic leukemia (42.8%) and 1 of 5 acute lymphocytic leukemia (20.0%). The days required for achieving the complete remission ranged from 23 to 78 days (median: 61) and the total doses of ACM used from 180 to 500 mg (median: 310), and the durations of complete remission from 11 to 28+ weeks (median: 21+). The untoward effects on digestive organs, such as nausea, vomiting and anorexia, and hematological toxicities were frequently seen; however, they were controlled by supportive treatment. Alopecia was not observed. Arrhythmia was recognized in one patient at the initiation of ACM infusion with complete remission without withdrawal of ACM. These results suggest that ACM is a potentially effective anthracycline antibiotic in the clinical management of acute leukemia.

**KEYWORDS:** aclacinomycin-A, leukemia, chemotherapy

---

\*PMID: 6449134 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **34**, (5), 349—354 (1980)

— BRIEF NOTE —

**TREATMENT OF REFRACTORY ACUTE LEUKEMIA  
WITH ACLACINOMYCIN-A**

Isao TAKAHASHI, Masamichi HARA, Tomiro ADACHI,  
Kazuko TAKAOKA, Makoto SAKANO, Miinyuh LAI,  
Fumikazu KOHI, Seiichi YORIMITSU, Masaaki  
TOKIOKA, Koichi KITAJIMA, Ikuro KIMURA  
and Hiroshi SANADA\*

*Second Department of Internal Medicine, (Director: Prof. I. Kimura) and*

*\*Department of Central Laboratory; Okayama University Medical  
School, Okayama 700, Japan*

*Received February 17, 1980*

**Abstract.** Twelve patients with refractory acute leukemia (7 patients with acute myelocytic leukemia and 5 patients with acute lymphocytic leukemia) were treated with a new anthracycline antibiotic, aclacinomycin-A (ACM). ACM was administrated by intravenous drip infusion at a dose of 20mg/day for 7 or 14 days and this was repeated after at least 7 days. Four of 12 patients (33.3%) achieved a complete remission; 3 of 7 acute myelocytic leukemia (42.8%) and 1 of 5 acute lymphocytic leukemia (20.0%). The days required for achieving the complete remission ranged from 23 to 78 days (median: 61) and the total doses of ACM used from 180 to 500 mg (median: 310), and the durations of complete remission from 11 to 28+\* weeks (median: 21+\*). The untoward effects on digestive organs, such as nausea, vomiting and anorexia, and hematological toxicities were frequently seen; however, they were controlled by supportive treatment. Alopecia was not observed. Arrhythmia was recognized in one patient at the initiation of ACM infusion with complete remission without withdrawal of ACM. These results suggest that ACM is a potentially effective anthracycline antibiotic in the clinical management of acute leukemia.

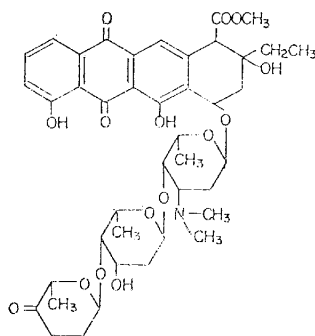
**Key words:** aclacinomycin-A, leukemia, chemotherapy.

Aclacinomycin-A (ACM) is a new anthracycline antibiotic isolated from the culture of streptomyces galilaeus MA 144-MI by Umezawa and his associates in Japan (1). In comparison with daunorubicin (DNR) and adriamycin (ADM), the structure of ACM is characterized by an ethyl group at C-9 instead of the acethyl or the hydroxyacethyl group, the methoxycarbonyl group at C-10 and the hexopyranoses (rhodosamine, 2-deoxyfucose and cinerulose) attached via

---

\* + indicates continued remission.

glycosidic linkage at C-7 (Fig. 1). ACM binds to DNA and disturbs the template activity for RNA and DNA polymerases (2, 3). The antitumor activity of ACM against L 1210 and P 388 leukemia mice is similar to DNR, but slightly less than ADM. ACM is effective against AH 41 ascitic hepatoma, which is refractory to DNR and ADM (4, 5). On the other hand, the acute cardiac toxicity of ACM in hamsters is less than 1/10 than that of ADM (4). Therefore, clinical application could be directed to different tumor spectrums with less cardiac toxicity as compared with other anthracyclines. Phase I and II studies have confirmed the effectiveness of ACM for the treatment of different types of solid tumors such as malignant lymphoma, breast cancer, carcinoma of the lung, gastric cancer and ovarian tumors (6-8).



molecular weight : 811.9

Fig. 1. Structure of Aclacinomycin-A

In this paper, the therapeutic effect of ACM on refractory acute leukemia was studied in order to evaluate its usefulness in the treatment of acute leukemia.

*Materials and methods.* Twelve patients with acute leukemia (7 patients with acute myelocytic leukemia and 5 patients with acute lymphocytic leukemia), who were refractory to conventional chemotherapeutic regimens, were entered in the present study (Table 1). They were 7 patients relapsed (4 patients with acute myelocytic leukemia and 3 patients with acute lymphocytic leukemia) and 5 patients with induction failure (3 patients with acute myelocytic leukemia and 2 patients with acute lymphocytic leukemia). The ratio of male to female was 4:8 and their ages varied from 21 to 73 years old. ACM, which was kindly supplied by Sanraku Ocean k.k. (Tokyo), was diluted in 200 ml of dextrose-electrolytes solution and administrated by intravenous infusion at a dose of 20 mg/day. ACM was administrated for 7 or 14 days and repeated after a resting period of at least 7 days. All patients were treated with ACM

TABLE 1. CHARACTERISTICS OF PATIENTS TREATED WITH ACLACINOMYCIN-A

Case no.	Age	Sex	Type of leukemia	Previous treatment
1	32	F	AML**	MP, DCMP, DCP, VCP, NCMF, NCP
2	25	F	AML*	NCMP, DCMP, N, AdC*P
3	63	F	AML*	NCMP, NAdVP, C*OA*P, IfC*, 'NC'
4	45	M	AML*	NCMP, DCMP, AdC*P, C*OA*F, NDCP
5	22	F	AML*	NCMP, NCDVP, AdC*P, CP, MEP
6	73	M	AML**	NCMP, NCDVP, DCP
7	59	M	AML**	C*, DCMP, DC*MP
8	21	F	ALL**	VP, DVP, VP+L-asparaginase, N
9	24	F	ALL*	VP, DVMP, NCDVP, DCVP, L-asparaginase, NCVP
10	32	F	ALL*	VP, CAMP, DVMP, VAMP, NCDVP, N <sub>6</sub> C*MP, L-asparaginase
11	66	M	ALL*	VP, L-asparaginase
12	33	F	ALL**	VP, DVMP, MTX+L-asparaginase

M: male; F: female; AML: acute myelocytic leukemia; ALL: acute lymphocytic leukemia; \*relapse \*\*induction failure; M: 6-mercaptopurine; P: prednisolone; D: daunorubicin; C and A\*: cytosine arabinoside; C': cycloctidine; C\*: behenoyl ara-c; O and V: vincristine; N: neocarzinostatin (2mg); N<sub>6</sub>: neocarzinostatin (6mg); Ad: adriamycin; C\* and E: cyclophosphamide; L-asparaginase: L-asparaginase; MTX and A: methotrexate; If: ifosfamide.

alone and the evaluation of the response was made according to Kimura's criteria (9).

**Results.** The clinical responses of 12 patients are shown in Table 2:

TABLE 2. CLINICAL RESPONSE TO ACLACINOMYCIN-A

	AML	ALL	Total
Total no. of patients	7	5	12
Complete remission	3	1	4
Complete remission rate (%)	42.8	20.0	33.3

AML, acute myelocytic leukemia; and ALL, acute lymphocytic leukemia

namely, 4 of 12 patients (33.3%) obtained complete remission. On the basis of type of leukemia, 3 of 7 patients with acute myelocytic leukemia (42.8%) and one of 5 patients with acute lymphocytic leukemia (20.0%) obtained complete remission. The days required for achieving complete remission ranged from 23 to 78 days (median: 61) and the total doses of ACM used from 180 to 500 mg in patients with complete remission (median: 310). The durations of complete remission were from 11 to 28+ weeks (median: 21+). It was noticeable that Case 9, which showed sinus tachycardia and substernal discomfort at the cumulative dose of 1,150 mg of DNR, could obtain the complete remission by ACM without any cardiac toxicity.

Toxic manifestations related to ACM are shown in Table 3. Gastrointestinal side effects such as nausea, vomiting and anorexia were most frequently seen. Transient arrhythmia (supraventricular premature beats) was recognized in one patient and vascular pain was complained of in 3 patients at the initiation of ACM infusion. Alopecia was not seen in any patients. Hematological toxicities such as leukopenia and thrombopenia were recognized in most patients (leukopenia, 10 of 12 patients and thrombopenia, 9 of 12 patients). Transient elevation of serum GOT was observed in 3 patients (up to 45 u, 85 u and 108 u) and of GPT in one patient (up to 46 u). All toxic signs were controlled by symptomatic treatment and did not require cessation of ACM.

TABLE 3. TOXIC SIGNS OF AGLACINOMYCIN-A

Toxic signs	No. of cases
Nausea	6/12 cases
Vomiting	6
Anorexia	6
Tachycardia	2
Arrhythmia (Supraventricular premature beats)	1
Vascular pain	3
Elevation of transaminase	
S-GOT	3/8 cases
S-GPT	1

*Discussion.* Two preparations of glycoside antibiotics of anthracycline antibiotics, DNR and ADM, were shown to useful chemotherapeutic agents for the treatment of malignant neoplasms in man (10-12). They have similar side effects such as alopecia, nausea and vomiting and cardiac toxicity becomes the dose-limiting factor in their clinical application. Therefore, further attempts have been made to explore new anthracycline antibiotics, which are more active and less toxic. In this respect, ACM promises well for the treatment of malignant neoplasms because of less cardiac toxicity. Phase I and II studies in Japan showed the effectiveness of ACM on different types of solid tumors. Mathé *et al.* used ACM in phase II trial in 22 patients with acute leukemia and lymphoma (13) and obtained complete remission in 4 of 9 patients with acute lymphocytic leukemia who were resistant to all previously available drugs, and 4 of 8 patients with stage V lymphosarcoma. Suzuki *et al.* reported a patient with refractory acute myelocytic leukemia who obtained complete remission with ACM (14). In the present trial of ACM, we obtained complete remission in 4 of 12 patients; 3 of 4 responders were suffering from acute myelocytic leukemia. *In vivo* studies using DNR-resistant L 1210 and ADM-resistant P 388 revealed that

ACM had cross-resistance to both agents, however, the clinical trial presented here suggests that ACM may be clinically effective in DNR-refractory acute myelocytic leukemia.

Of the toxic effects of ACM, gastrointestinal side effects were most frequently seen. ACM has less cardiac toxicity than DNR and ADM. In the present trial one patient, who complained of sinus tachycardia and substernal discomfort at a total dose of 1,150 mg of DNR, obtained complete remission with ACM without any cardiac manifestations. On the other hand, in one patient, a 66 years old male suffering from acute lymphocytic leukemia, supra-ventricular premature beats were recognized. However, they were transient and did not need any specific treatment. He obtained complete remission without having to cease ACM.

The data presented in this report indicate the effectiveness of ACM on refractory acute leukemia, not only on acute lymphocytic leukemia but also on acute myelocytic leukemia. Further studies are in progress to evaluate the superiority of ACM than other anthracyclines. We will try to evaluate its effectiveness in combination with other antileukemic agents such as cytosine arabinoside.

#### REFERENCES

1. Oki, T., Matsuzawa, Y., Yoshimoto, A., Numata, K., Kitamura, I., Hori, S., Takamatsu, A., Umezawa, H., Ishizaka, M., Naganawa, H., Suda, H., Hamada, M. and Takeuchi, T.: New antitumor antibiotics, aclacinomycin A and B. *J. Antibiot. (Tokyo)* **28**, 830-834, 1975.
2. Yamaki, H., Suzuki, H., Nishimura, T. and Tanaka, N.: Mechanism of action of aclacinomycin A. I. The effect on macromolecular synthesis. *J. Antibiot. (Tokyo)* **31**, 1149-1154, 1978.
3. Misumi, M., Yamaki, H., Akiyama, T. and Tanaka, N.: Mechanism of action of aclacinomycin A. II. The interaction with DNA and with tubulin. *J. Antibiot. (Tokyo)* **32**, 48-52, 1979.
4. Hori, S., Shirai, M., Hirano, S., Oki, T., Tsukagoshi, S., Ishizuka, M., Takeuchi, T. and Umezawa, H.: Antitumor activity of new antibiotics, aclacinomycin-A and its analogs, and their toxicity. *Gann* **68**, 685-690, 1977.
5. Oki, T.: New anthracycline antibiotics. *J. Antibiot. (Tokyo)* **30**, suppl., 70-84, 1977.
6. Oka, S.: A review of clinical studies on aclacinomycin A-Phase I and preliminary phase II evaluation of ACM-. *Sci. Rep. Res. Inst. Tohoku Univ.* **25**, 37-49, 1978.
7. Ogawa, M., Inagaki, J., Horikoshi, N., Inoue, K., Chinen, T., Ueoka, H. and Nagura, E.: Clinical study of aclacinomycin A. *Cancer Treat. Rep.* **63**, 931-934, 1979.
8. Sakano, T., Okazaki, N., Ise, T., Kitaoka, K. and Kimura, K.: Phase I study of aclacinomycin A. *Jpn. J. Clin. Oncol.* **8**, 49-53, 1978.
9. Kimura, K.: Chemotherapy of acute leukemia with special reference to criteria for evaluation of therapeutic effect. In *Advances in Chemotherapy of Acute Leukemia*. A Seminar on Chemotherapy of Acute Leukemia under the Japan-U. S. Cooperative Science Program, Sept. 27-28, Bethesda, Md., USA, pp. 21-23, 1965.
10. Di Marco and Lenaz, L.: Daunomycin and adriamycin. In *Cancer Medicine*, ed. J. F. Holland and E. Frei, III Lea and Febiger, Philadelphia, pp. 826-835, 1973.

11. Bernard, J., Paul, R., Boiron, M., Jacquillat, C. and Maral, R.: *Rubidomycin: A New Agent Against Cancer*, Springer, Berlin. 1969.
12. Blum, R.H. and Carter, S.K.: Adriamycin: A new anti-cancer drug with significant clinical activity. *Ann. Int. Med.* **80**, 249, 1974.
13. Mathé, G., Bayssas, M., Gouveia, J., Dantchev, D., Ribaud, P., Machover, D., Misset, J. L., Schwarzenberg, L., Jasmin, C. and Hayat, M.: Preliminary results of a phase II trial of aclacinomycin in acute leukaemia and lymphosarcoma. *Cancer Chemother. Pharmacol.* **1**, 259-262, 1978.
14. Suzuki, H., Kakinuma, Y., Kawashima, K., Morishima, Y., Tanimoto, M., Kato, Y., Watanabe, E., Ogata, K., Kobayashi, M., Takeyama, H., Ezaki, K., Koderu, Y., Ohno, R., Yamada, K. and Kawabe, M.: Successful treatment with aclacinomycin A in a case of acute myeloblastic leukemia refractory to conventional multicombination chemotherapy. *Cancer Chemother.* **6**, 191-196, 1979.

**Erratum:** In the issue of *Acta Medica Okayama*, Vol. 34, No. 4, the legends to Figs. 1 and 2 in the article "Immunochemotherapy of Gastric Cancer with Levamisole" by Miwa, H. *et al.* on pages 277 and 278 should be interchanged.